REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 1-16, 19, 38-41 and 48-66 will be pending in the application subsequent to entry of this amendment.

Discussion of New and Amended Claims

Although there are no formalities objections or rejections directed to the claims as previously examined, claims 48 and 49 are amended and claims 51 – 66 directed to disclosed but previously unclaimed subject matter are added. The amendments to the claims are detailed below and the basis for each amendment and/or new claim is indicated parenthetically.

Claims 48 and 49 have been amended to specify that a therapeutic plasma concentration of 0.4 to 5 ng/ml (page 18, line 3) is produced within 0.5 to 20 minutes (page 17, line 28) and maintained for up to 6 hours (page 18, line 7).

New claims 51 and 52 have been added which are dependent upon claims 49 and 48, respectively, and relate to a therapeutic plasma concentration of 0.4 ng/ml being attained within 2 to 15 minutes and maintained for 2 to 4 hours (page 18, lines 8 to 10).

New claims 53 to 55 have been added which relate to solutions comprising 0.5 to 8 ng/ml of buprenorphine or a salt or ester thereof (page 11, line 8), 1 to 6 ng/ml of buprenorphine or a salt or ester thereof (page 11, line 9) and buprenorphine hydrochloride (page 11, lines 5 to 6), respectively.

New claim 56 has been added which relates to a process for preparing the solution of claim 16 (page 4, lines 19 to 25).

New claims 57 and 58 have been added which relate to a nasal delivery device and a nasal spray device which comprises the solution of claim 16 (page 17, lines 2 to 3).

New claim 59 has been added which relates to a method of inducing analgesia using a solution of claim 16 (page 5, lines 9 and 10).

New claims 60 to 66 have been added. Claims 60 to 62 and 64 to 66 are equivalent to claims 53 to 55 and 57 to 59 and have the same basis. Claim 63 has basis from page 4, lines 24 to page 5, line 5.

The issues raised in the Official Action are now address in the order presented.

Priority Claim

The Examiner contends that certified copies of the priority applications have yet to be filed. However, certified copies of the two priority applications were filed in the International stage and should have been forwarded by the IB to the US Patent Office. Applicants have thus completed all actions necessary at the International Bureau to complete their claim for benefit of priority. Also, contrary to the examiner's (apparent) suggestion, a certified copy of the International application is not required as this filing is under 35 USC §371, as the Office and the filing receipt indicate.

Specification

The title of the application is amended to "Buprenorphine Formulations for Intranasal Delivery" in accordance with the Examiner's comments.

Background to the Present Invention

As a general comment, buprenorphine is an analgesic, but with the major disadvantage when used in the treatment of pain of poor oral or sublingual bioavailability for systemic action.

This results in relatively low maximum plasma concentrations and a relatively long time after administration for the maximum plasma concentration to be reached, e.g. 3 ½ hr after administration for commercially available sublingual formulations.

This results in turn in a slow onset of analgesia after administration and a lower than optimum level of analgesia.

The bioavailability for systemic action may be improved in humans by nasal administration, resulting in higher maximum plasma concentrations and a shorter time after administration for the maximum plasma concentration to be reached.

However, with all known formulations the release of the buprenorphine is not well sustained with the major disadvantage when used in the treatment of pain of relatively rapid decay in plasma concentrations after the maximum plasma concentration is reached.

This results in analgesia that is not well sustained.

The present invention thus sets out to provide nasal buprenorphine compositions for systemic action with relatively high maximum plasma concentrations at a relatively short time after administration which are relatively well sustained, resulting in the major advantage when used in the treatment of pain of:

i) relatively rapid onset of analgesia after administration,

ii) a closer to optimum level of analgesia and/or

iii) analgesia that is well sustained.

One of the ways in which this profile is achieved is to provide a liquid which is sufficiently viscous and/or gels on the mucosa to hold the drug in situ.

Response to Prior Art-Based Rejections

The Action includes for rejections based upon prior art. To the extent the examiner may consider these rejections pertain to pertain to the new and amended claims presented above, the rejections are traversed. Turning to the points of the action in order:

Claims 48 to 50

The subject matter of these claims in their amended form is novel over the formulations of Eriksen.

Independent claims 48 and 49 require that within 0.5 to 20 minutes a therapeutic plasma concentration of 0.4 to 5 ng/ml is reached which is maintained for up to 6 hours. It will be seen from Table 3 and Fig. 1 of Eriksen that although the initial concentration is reached in the time period, by 6 hr it has decayed to 0.23.

New dependant claims 51 and 52 require that a therapeutic plasma concentration of 0.4 ng/ml or more is produced within 2 to 15 minutes and is maintained for 2 to 4 hours. Again, Eriksen discloses levels that fall to 0.34 in 4 hr. In contrast the present buprenorphine formulations (Figs.1 - 3) maintain a level above 0.4 ng/ml.

The subject matter of these claims in their new form is thus novel over the formulations of Eriksen.

Although no §103(a) rejection of claims 48 to 50 has been made, it is commented on here for completeness. Eriksen fails to disclose the present buprenorphine formulations, since its resultant plasma level fall to 0.34 in 4 hr.

Eriksen is thus not a document that would be considered by one skilled in the art seeking to provide a buprenorphine composition which provides:

i) relatively rapid onset of analgesia after administration,

ii) a close to optimum level of analgesia and

iii) analgesia that is well sustained.

Even if Eriksen were considered, it nowhere teaches to adjust its formulations to achieve the major advantages of relatively high maximum plasma concentrations at a relatively short time after administration which are relatively well sustained.

Eriksen thus does not render these claims obvious.

Claims 1-15, 38-39 and 41

A §103 rejection of claims 1 – 15, etc has been made over Eriksen as the primary citation viso Watts, Reich and Nairn. Its formulations differ from the present buprenorphine - pectin formulation as follows:

i) the presence of dextrose and the absence of pectin with a DE of less than 50% (at 5 – 40 mg),

ii) a pH of about 7, and not 3 – 4.2,

iii) no teaching of the absence of divalent cations, and

iv) no teaching that the formulations of the citation gel on the nasal mucosa.

In regard to point iii), Eriksen does not specifically teach to use deionised or distilled water, which is the only type of water in routine use that does not contain divalent cations. If any assumption is to be made, it must be that the water is tap water, which routinely contains divalent metal ions.

To recap, the present invention sets out to provide nasal buprenorphine compositions for systemic action relatively high maximum plasma concentrations at a relatively short time after administration which are relatively well sustained, resulting in the major advantage when used in the treatment of pain of :

i) relatively rapid onset of analgesia after administration,

ii) a closer to optimum level of analgesia and/or

iii) analgesia that is well sustained.

For the reasons set out for claims 48 to 50 above, Eriksen fails to teach formulations that have the combination of i) and ii) with iii). It is thus not a document that would be considered by one skilled in the art seeking to provide a buprenorphine composition which provides this combination.

Even if Eriksen were used, Watts nowhere teaches to adjust the formulations of Eriksen

in the expectation of providing a nasal buprenorphine composition with a systemic activity profile with:

i) a relatively rapid onset of analgesia after administration,

ii) a closer to optimum level of analgesia, and

iii) analgesia that is well sustained.

Indeed, Watts teaches directly away from formulations with such an activity profile. The thrust of Watts is entirely towards ensuring prolonged retention of the formulations in the nasal cavity, and sustained release of a drug to the nasal mucosa.

It is entirely silent as to providing an activity profile which also enhances transmucosal absorption of a drug to give a relatively high maximum plasma concentration at a relatively short time after administration, **as well as** relatively well sustained plasma levels. Again, the thrust of Watts is entirely away from such a profile. Watts teaches that its formulations may be used for local and systemic administration.

If for local administration, Watts teaches that the formulation **should not** enhance transmucosal absorption of a drug into systemic circulation, i.e. it **should not** give rise to any significant plasma concentration, still less at a short time after administration (p. 3, ll. 21 on).

If for systemic administration, Watts teaches that its compositions are used to control the plasma concentrations of drugs, in particular to retard the transmucosal absorption of drugs which are readily absorbable, and where peak plasma concentrations are to be avoided (p.14, ll. 12 on). In all aspects it teaches away from sustained plasma levels.

Again, the thrust of the examples of Watts relate entirely to formulations which **do not** enhance transmucosal absorption of a drug.

Thus, even if Eriksen were used as a basis for his quest, Watts is not a document that would be considered by one skilled in the art seeking to adjust the formulations of Eriksen to retain relatively high maximum plasma concentrations at a relatively short time after administration whilst ensuring that these concentrations are relatively well sustained.

Watts clearly teaches that the changes will result in a reduction in absorption and a consequent increase in the time to reach therapeutic systemic plasma levels and/or a reduction in such levels, i.e. away from these advantageous aspects of the profile of Eriksen.

The combination of Eriksen viso Watts thus cannot render these claims obvious.

The §103 rejection of claims 2 – 15, etc has been made over Eriksen as the primary citation viso Reich and Nairn. These rejections stand or fall with claim 1, so no further comment is made here.

Claim 16

A §103 rejection of claim 16 has been made over Eriksen as the primary citation viso Koochaki. Its formulations differ from the present buprenorphine - pectin formulation as follows:

a) the presence of dextrose and the absence of chitosan and hydroxypropylmethylcellulose,

b) a pH of about 7, and not 3 – 4.8.

For the reasons set out for claims 48 to 50 above, Eriksen is not a document that would be considered by one skilled in the art seeking to provide a buprenorphine composition which provides the combination of :

i) a relatively rapid onset of analgesia after administration,

ii) a closer to optimum level of analgesia, and

iii) analgesia that is well sustained.

Even if Eriksen were used, Koochaki nowhere teaches to adjust the formulations of Eriksen in the expectation of providing a nasal buprenorphine composition with the desired activity profile.

The thrust of Koochaki is towards the solving the problem that it perceives with jelly and spray formulations for delivering drugs in the nasal cavity, viz the lack of sustained presence of the drug on the nasal mucosa (as symptomized by 'roll-back'), and the consequent lack of sustained release.

It must be noted that these include prior art formulations that may be used for nasal administration, which comprise chitosan and/or a cellulosic.

Koochaki teaches that the only solution to this problem is to avoid any liquid and/or gel compositions and methods of treatment entirely, and to use only solid powder formulations. That is, it teaches directly away from the present liquid and/or gel formulations with the desired activity profile.

Thus, even if Eriksen were used as a basis for his quest, Koochaki is not a document that

would be considered by one skilled in the art seeking to adjust the formulations of Eriksen.

The combination of Eriksen viso Koochaki thus cannot render claim 16 obvious.

Claim 19

The §103 rejection of claim 19 has been made over Eriksen as the primary citation viso Williams. Its formulations differ from the present buprenorphine - pectin formulation as follows:

i) the presence of dextrose and the absence of chitosan and a polyox, and

ii) a pH of about 7, and not 3 – 4.8.

For the reasons set out for claims 48 to 50 above, Eriksen is not a document that would be considered by one skilled in the art seeking to provide a buprenorphine composition for **systemic** action with relatively high maximum plasma concentrations at a relatively short time after administration which are relatively well sustained, resulting in the major advantage when used in the treatment of pain of:

i) relatively rapid onset of analgesia after administration,

ii) a closer to optimum level of analgesia and/or

iii) analgesia that is well sustained.

Even if Eriksen were used as a basis for this quest, Williams nowhere teaches to adjust the formulations of Eriksen in the expectation of providing a nasal buprenorphine composition with the desired activity profile **systemically.**

There is no unambiguous teaching in Williams of formulations which comprise the combination of a chitosan and a polyox, or of a chitosan – polyox composition with the desired activity profile.

The thrust of Williams is entirely towards formulations for delivering drugs to mucosa (e.g. nasal mucosa) for local anaesthesia, with a lack of or at most negligible transmucosal absorption of anaesthetic and consequently no or a negligible plasma concentration.

Williams clearly teaches directly away from formulations with relatively high maximum plasma concentrations at a relatively short time after administration.

Thus, even if Eriksen were used as a basis for his quest, Williams is not a document that would be considered by one skilled in the art seeking to adjust the formulations of Eriksen.

The combination of Eriksen viso Williams thus cannot render claim 19 obvious.

Response to Provisional Double Patenting and Double Patenting Rejections

The Action includes three double patenting rejections two of which are provisional. All of these rejections and provisional rejections are regarded as being untimely or at least not ready for resolution considering the lack of allowable subject matter in the subject application, at least as of the date of this response.

Since the examiner has made two double patenting rejections of various claims in sections 40 – 55 of the action provisional both over co-pending '315 citation, applicants' response to these points will be held in abeyance until the scope of the relevant claims in the '315 is determined and claims are allowed or indicated to be allowable.

The examiner has also made a non-provisional obviousness-type double patenting rejection of various claims in sections 56 – 60 of the action over US 6,387,917 (Illum). This rejection is incorrect.

The thrust of Illum is entirely to compositions for parenteral or non-parenteral administration of a systemically acting opioid analgesic in which the solubilizing methanesulphonate anion enhances absorption of a drug. In particular, its examples are entirely towards the use of that salt of morphine. There is no unambiguous teaching in Illum of formulations for the nasal cavity that comprise buprenorphine or a salt thereof. There is no teaching to select buprenorphine from the general opioids and to provide nasal compositions of it or its salts which give a relatively high maximum plasma concentration at a relatively short time after administration, **as well as** relatively well sustained plasma levels.

Illum is thus not a document that would be considered by one skilled in the art seeking to provide a buprenorphine composition which provides the major advantage of:

i) relatively rapid onset of analgesia after administration,

ii) a close to optimum level of analgesia and

iii) analgesia that is well sustained, in the reasonable expectation of success.

Illum thus does not render the relevant present claims obvious.

Summary

It is submitted that the application is in order for allowance. Favorable reconsideration of this application is requested. Should the examiner require further information please contact the undersigned.

Respectfully submitted,

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